PROTECTION BY PREGNANCY AGAINST THE DEVELOPMENT OF "INFARCTOID CARDIOPATHY" AND NEPHROCALCINOSIS

BY

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NUMEROUS earlier publications have dealt with the possible influence of pregnancy and of sex hormones upon the development of clinical or experimental cardiovascular diseases, but the relevant data are rather difficult to interpret (Selye, 1950; Stamler, Katz and Pick, 1954; Selye, Heuser and Horava, 1951–1955/56). More recent experiments on rats showed, however, that dihydrotachysterol, which produces severe arteriosclerosis of the Mönckeberg type in non-pregnant rats, is well tolerated during pregnancy (Selye, 1957).

During the past year, it has been demonstrated that certain corticoids (especially the highly potent 9-halogenated compounds) can so condition the cardiac muscle of rats that the oral administration of an excess of sodium phosphate regularly produces infarct-like, massive necroses in the myocardium. This is usually, but not always, associated with nephrocalcinosis (Selye and Renaud, 1957; Selye, 1958a). The entire literature concerning this "infarctoid cardiopathy", including its possible relationship to the spontaneous cardiac infarcts of man, has been surveyed elsewhere (Selye, 1958b).

The object of this communication is to report upon experiments which demonstrate that pregnancy offers a definite protection against the infarct-like phosphate-steroid-cardiopathy and the accompanying nephrocalcinosis. This finding is reminiscent of the inhibitory effect that gestation exerts upon the arteriosclerosis normally induced by dihydrotachysterol.

METHOD

Our experiments were performed on two groups, each consisting of 10 adult, female rats of the Sprague-Dawley strain, with an average initial body-weight of $315 \pm 3 \cdot 3$ g. and $228 \pm 3 \cdot 8$ g. respectively. The controls exhibited normal sexual cycles, while the experimental animals were 14- to 15-days pregnant at the beginning of the experiment.

Both groups were treated with 400 mg. of monosodium phosphate ($NaH_2PO_4 \cdot H_2O$) in 4 ml. of water, twice daily, by stomach tube. In addition, they received 250 μg. of 2α-methyl-9α-chlorocortisol (Me-Cl-COL), in the form of microcrystals of its acetate suspended in $0 \cdot 2$ ml. of water, once daily, subcutaneously. This combined phosphate-steroid treatment had previously been shown to be highly efficacious in eliciting the infarctoid cardiopathy.

Throughout the experiment, the rats of both groups were kept exclusively on the laboratory food, "Purina Fox Chow" of the Ralston Purina Company, and tap water.

The hearts and kidneys of all the animals which either died spontaneously or were killed at the end of the experiment were fixed in neutral formalin, for subsequent embedding in paraffin and staining with haematoxylin-phloxine (for the appraisal of general structure) as well as with von Kossa's silver nitrate technique (for the histochemical demonstration of calcium). The severity of the cardiac necroses and of the nephrocalcinosis was gauged in terms of an arbitrary scale of 0 to 3.

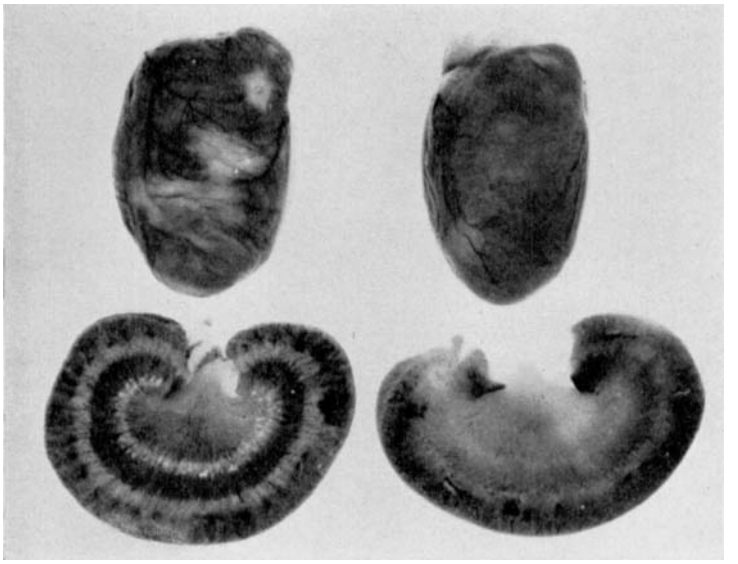

FIG. 1

Macroscopic appearance of the outer surface of the heart (top) and the cut surface of the kidney in a non-pregnant (left) and a pregnant animal, both of which received the same dose of Me-Cl-COL and NaH_2PO_4. The light patches of "infarctoid cardiopathy" and the concentric lines of nephrocalcinosis, that developed under the influence of this treatment in the non-pregnant control, are absent in the pregnant animal.

FIG. 2

Cut surface of the hearts shown in Figure 1. The miliary, infarct-like, white, necrotic patches in the non-pregnant animal (top) are distributed throughout both ventricles and are particularly conspicuous near the apex of the heart. No such lesions are observable in the interior of the pregnant animal's heart.

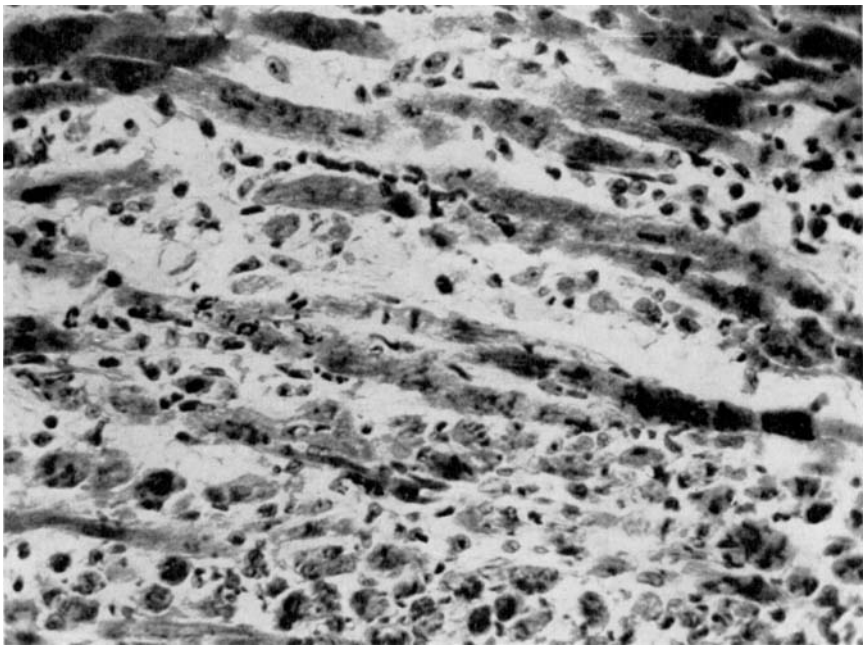

FIG. 3

Histological aspect of a necrotic patch in the heart of the non-pregnant animal shown in Figure 1. The muscle fibres throughout this field are in various stages of disintegration and the focus is invaded by histiocytes and polymorphonuclear leukocytes. Haematoxylin-phloxine. · 350.

Results

Between the third and fourth day of treatment, all the non-pregnant controls began to lose weight. Their fur became shaggy and they exhibited manifest clinical signs of cardiac insufficiency, such as cyanosis and dyspnoea. Five of these rats died between the third and sixth day of treatment, while the sixth had to be killed on the eighth day, because it was manifestly moribund.

Autopsy of these control animals revealed the characteristic, large, yellowish patches of myocardial necrosis, and intense nephrocalcinosis (Figs. 1 and 2). Histological study of the tissues showed that the myocardial lesions consist of necrotic patches, within which the muscle fibres first disintegrate, and are then invaded and replaced by histiocytes, polymorphonuclear cells and, eventually, a connective tissue scar (Fig. 3). In the kidney, numerous calcified cylinders were detectable, especially at the cortico-medullary junction line (Fig. 2).

In contrast, all of the pregnant rats remained perfectly healthy and their pregnancy continued without complication.

On the sixth day, when 50 per cent of the controls had died, the treatment of the surviving pregnant animals was discontinued; they all delivered healthy young, at approximately the normal time.

After delivery, the animals were killed, and histological study of their organs revealed no sign of phosphate-steroid-cardiopathy in the mothers or in their young. Also, there was no nephrocalcinosis in the newborn, although one of the mothers showed traces of renal calcification.

Discussion

It is evident, from these observations, that pregnancy can very effectively protect the rat against the development of the infarct-like cardiac lesions and the nephrocalcinosis that normally occur under the influence of combined treatment with Me-Cl-COL plus sodium phosphate. It remains to be seen whether the factor responsible for this protection against the infarctoid cardiopathy is the same as that which, in pregnant animals, prevents the development of arteriosclerosis after dihydrotachysterol treatment. Experiments are now under way to determine whether the protection against the infarctoid cardiopathy is due to the embryo, the placenta, or some (possibly hormonal) change in the maternal organism. The possibility must be considered that this kind of protection may be related in some way to the relatively low incidence of spontaneous infarcts in women.

Summary

Experiments on rats indicate that pregnancy offers considerable protection against the infarct-like cardiac necroses and the nephrocalcinosis that are normally produced by combined treatment with NaH_2PO_4 and certain corticoids such as 2α-methyl-9α-chlorocortisol (Me-Cl-COL).

The possible clinical implications of this finding are discussed.

Acknowledgments

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